UNITAID

2015

Review of the Velpatasvir Patent Landscape:

A scoping report

JULY 2015

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World Health Organization

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Abbreviations

API	active pharmaceutical ingredient
DAA	direct acting antiviral
HCV	hepatitis C virus
HIV	human immunodeficiency virus
PCT	Patent Cooperation Treaty
RNA	ribonucleic acid

I. INTRODUCTION

Hepatitis C virus (HCV) is a major global health problem. With 80 – 150 million people worldwide chronically infected with the virus, the prevalence of HCV is higher than that of the human immunodeficiency virus (HIV). It is estimated that, worldwide, 4 – 5 million people are coinfected with HIV and HCV. Each year, 500 000 – 700 000 people die of HCV-related liver disease, and evidence indicates that the HCV burden is increasing.[1,2] While the HCV epidemic is global in scope, the HCV burden varies considerably between countries.

The virus has six primary genotypes. Genotypes 1 and 3 are the most prevalent, accounting respectively for 46% and 30% of HCV cases worldwide. Together, genotypes 2, 4 and 6 represent around 23% of HCV cases, while genotype 5 accounts for less than 1%.[3]

Efforts to treat HCV have historically been hampered by suboptimal and inadequate treatments. However, the development of direct-acting antivirals (DAAs) has dramatically improved HCV treatment prospects and has altered the standard of care. Several new DAAs that do not require Peg-IFN were launched in late 2013 and in 2014, and a number of other DAAs are in development.

These DAAs generate cure rates that approach or exceed 90%. Some combination regimens may have pan-genotypic efficacy, which would simplify treatment and monitoring. UNITAID's Hepatitis C Medicines Technology and Market Landscape, published in February 2015, identified Gilead's investigational compound GS-5816 – velpatasvir – as being of particular interest, as it is potentially pan-genotypic.

In view of velpatasvir's potential role in future treatment, this report explores the patent landscape of velpatasvir.

1 Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
2 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(117–71).
3 Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2014;61(1):77–87.

II. METHODOLOGY

Relevant patents and patent applications were identified by searching patent and non-patent databases, namely: PatBase, TotalPatent, SciFinder and Google patent. Searches were carried out using keywords, semantic searches and structure searches.

For each of the most relevant patents or applications, the equivalents were identified (INPADOC family) and the legal status of each of the equivalents was checked on the websites of the relevant patent offices. The countries listed in Annexes 1 and 2 represent those for which INPADOC data is available.

Data for Thailand and Viet Nam were checked by local patent attorneys at the local patent office. In Pakistan, the local patent office provided a search for equivalents to help prepare this report.

The searches were carried out in January 2015. The analysis of the identified patents and patent applications was undertaken on the basis of the European patent/application, unless otherwise indicated.

Caveat: It is important to note that the patent status of a given product in a given country may change and that data may therefore become outdated. It is advisable always to check with the relevant national or regional patent office for the most up-to-date information on the status of a given patent or patent application.

This report was prepared by Andrew Brown and Amel Garbi (Pharmathen), with input from Karin Timmermans (UNITAID). The patent searches were conducted by Amel Garbi, Pharmathen.

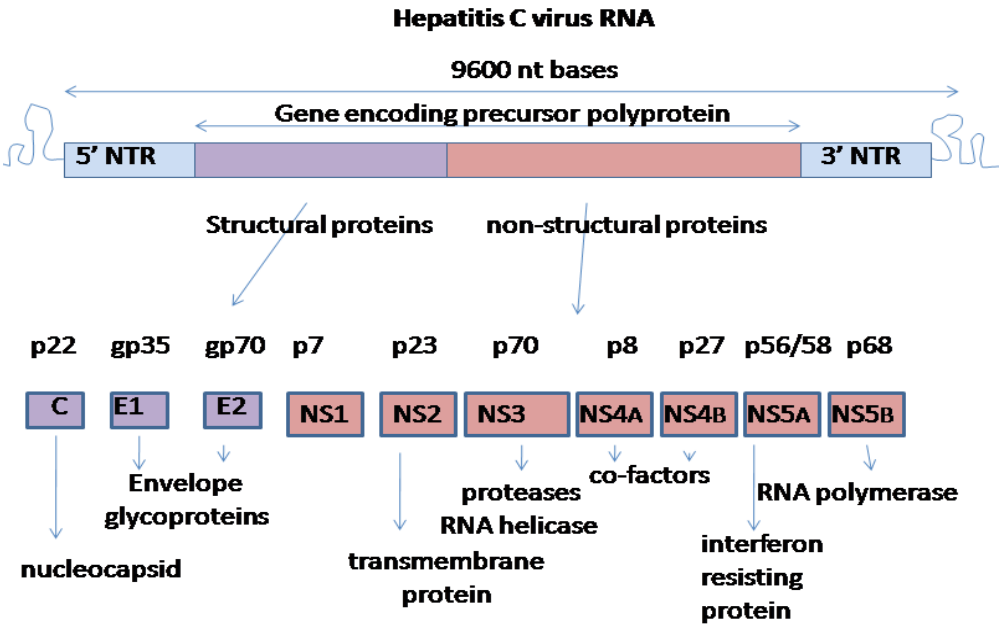
The following reviewers provided valuable input, comments and suggestions on all or part of a draft version of this report: Peter Beyer, Pascale Boulet, Yao Cheng, Leena Menghaney and Maica Trabanco.

III. BACKGROUND

Hepatitis C virus

The hepatitis C virus is a small (55 – 65 nm), enveloped, positive-sense single-stranded RNA virus of the *Flaviviridae* family. The virus consists of three structural proteins (core, E1 and E2), the ion channel protein p7 and 6 non-structural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B) (see Figure 1). Each of these proteins plays a role in HCV entry, infection, replication or maturation and is therefore a potential target for medicines.

Figure 1. Hepatitis C virus RNA



Source: Graham Colm.

DAAs block viral production by directly inhibiting one or more steps of the HCV replication cycle. DAAs can be divided into categories – notably NS3/NS4A serine protease inhibitors, NS5A complex inhibitors and NS5B RNA polymerase inhibitors (both nucleoside and non-nucleoside).

NS5A is a 447 amino acid, zinc-binding phosphoprotein that is believed to play a key role in HCV RNA replication. NS5A exists in 2 forms: a hypophosphorylated p56 and a hyperphosphorylated p58 based on electrophoric mobility. NS5A is essential to HCV genome replication.

Velpatasvir (GS-5816) is an NS5A inhibitor that is currently in clinical development.

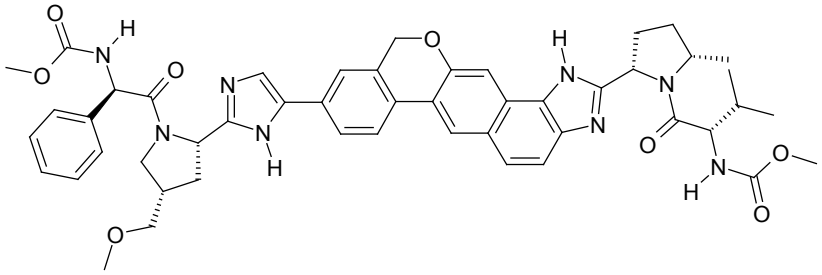
Gilead is developing a once-daily, fixed-dose combination (FDC) tablet of sofosbuvir (400 mg) with velpatasvir (100 mg), and has a triple-drug combination of sofosbuvir, velpatasvir and GS-9857 in phase II trials.[4]

Velpatasvir

The first-generation HCV NS5A inhibitors such as ledipasvir are attractive because of the low dose required to inhibit HCV replication, but they show a low barrier to resistance and have little or no antiviral effect on some common NS5A polymorphs and NS5A-inhibitor resistance-associated variants.

The second-generation NS5A inhibitors reportedly display improved potency. Velpatasvir demonstrated potent activity against genotypes 1–6 in early studies, displaying low EC_{50} values (6–130 pM).[5] The chemical structure of velpatasvir is shown in Figure 2.

Figure 2. Structure of velpatasvir



Chemical name:

methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2- [(methoxycarbonyl)amino]-2-phenylacetyl}- 4-(methoxymethyl)pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-1,11-dihydro[2]benzopyrano[3',4':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate.

Molecular formula: $C_{49}H_{54}N_8O_8$

Molecular weight: 883 g/mol

CAS registry number: 1377049-84-7

4 Gilead announces data for investigational, all-oral, pan-genotypic three-drug regimen of sofosbuvir, GS-5816 and GS-9857 for chronic hepatitis C. Business Wire, 23 April 2015.

5 Report by Gilead Sciences, USA. Conference report of the 48th Annual Meeting of the European Association for the Study of the Liver, 24–28 April 2013, Amsterdam, Netherlands.

IV. OVERVIEW OF VELPATASVIR PATENTS

Three patents and/or patent applications related to velpatasvir (GS-5816) have been identified as appearing to be the most relevant. These three patents/applications, and a divisional patent/application, include the patent/application covering the compound per se, as well as processes for preparing it and formulations and combinations that include it.

Patent 1 may be able to block the production, import, marketing and use of generic versions of velpatasvir, depending on the claims allowed/granted.

Patent 2 is the main patent; it would likely block the production, import, marketing and use of generic versions of velpatasvir in countries where it is in force.

Patent 3 would likely hamper the production, import, marketing and use of generic versions of the combination of sofosbuvir/velpatasvir (as well as sofosbuvir/ledipasvir) if granted.

A brief overview of the three most relevant patents and/or applications can be found in Table 1. More extensive information is provided in section V and Annex 1.

Table 1. Overview of key patents on velpatasvir

	Application/patent number	Applicants	Filing date	Comments
1.	EP-A-2640719 WO-A-2012/068234	Gilead Pharmasset (USA)	16.11.2011	Broad compound patent (Markush formula). Likely to constrain generic market entry where it is in force.
2.	EP-B-2635588 WO-A-2013/075029	Gilead Pharmasset (USA)	16.11.2012	Basic compound patent; claims the API. Likely to constrain generic market entry where it is in force.
	Application EP-15156617.1 Divisional application	Gilead Pharmasset (USA)	16.11.2012	Not yet published
3.	WO-A-2014/185995	Gilead Pharmasset (USA)	30.01.2014	Combination sofosbuvir/velpatasvir with or without another anti-HCV agent.

In the European phase, the claims of the PCT application of patent 1 were amended and limited to a category of compounds that does not include velpastavir. Thus, in the European Union this application is not relevant for velpatasvir.

In other countries, it will be important to check at the national level whether and how the claims of the original PCT application may have been amended. This would be particularly important in countries where patent 2 has not been filed or has not been granted since, in these countries, patent 1 may, or may not, be the blocking patent, depending on the actual claims.

V. ANALYSIS OF VELPATASVIR PATENTS/APPLICATIONS

Patent 1

Title: Antiviral compounds

WO-A-2012068234 (*Gilead Pharmasset (US), filed 16.11.2011*); **EP-A-2640719**

Summary

The PCT application is for a broad compound patent that claims compounds of Markush formula (I). This Markush formula pertains to five different classes of compounds. The first class includes velpatasvir.

This patent would likely block generic market entry in the countries where it is in force.

Description

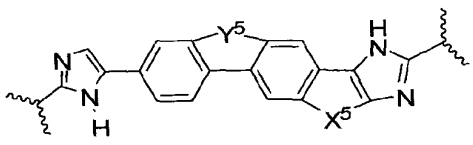
The PCT application relates to heterocyclic compounds of general formula (I) or a pharmaceutically acceptable salt thereof for use as antiviral agents in treatment of HCV.

$$E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}\ W^{1a}\text{-}P^{1b}\text{-}C(=O)\text{-}\ V^{1b}\text{-}\ E^{1b} \qquad \textbf{(I)}$$

The compounds falling within the scope of the claims for which protection is sought have the following structural feature: a core W^{1a} which contains at least 2 hetero rings, and is selected from formulas A, B, C, D and E. The core W^{1a} links 2 moieties $E^{1a}\text{-}V^{1a}\text{-}C(=O)\text{-}P^{1a}\text{-}$ and $E^{1b}\text{-}V^{1b}\text{-}C(=O)\text{-}P^{1b}\text{-}$.

Thus, a wide range of compounds, falling in five classes, is claimed.

The first class consists of antiviral compounds of formula (I) wherein W^{1a} is of formula A:



A

in which Y^5 is $\text{-O-CH}_2\text{-}$ or $\text{-CH}_2\text{-O-}$ and X^5 is $\text{-CH}_2\text{-CH}_2\text{-}$ or -CH = CH-.

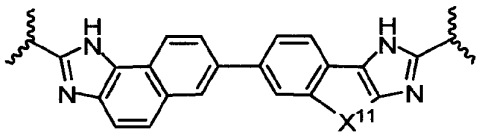
Such compounds have a pentacyclic ring system linked to an imidazole ring. Both the pentacyclic ring system and the imidazole ring are substituted by a substituted pyrrolidine.

Velpatasvir falls within the scope of this claimed class of compounds in which Y^5 is $\text{–CH}_2\text{-O-}$ and X^5 is –CH = CH-. Velpatasvir is specifically claimed at claim 41 of the PCT application (8^{th} compound, p. 1311, within a list of 23 compounds characterized by their chemical structure).

The PCT application has 324 claims, of which 19 are independent.

The claims encompass a large number of compounds and, according to the international preliminary report on patentability, the number of alternative compounds falling within the scope of the present claims is such that it is unlikely that all of them possess the claimed activity. The claims should represent a reasonable generalization of the examples given in the description and in the examples section. According to the international preliminary report, the applicants failed to provide supporting evidence that all the compounds can be used for the claimed activity.

In the European phase, the compounds claimed were limited to the second class of compounds covered by the original PCT application – i.e. the compounds of invention 2, the subject matter of original claim 3: compounds where W^{1a} is of formula B and in which one or both pyrrolidine groups have a methoxymethyl substituent (amended claim of 14.01.2014).



B

Additionally, the terms alkyl and cycloalkyl have been redefined in accordance with the meaning given in the description (i.e. C_{1-18} alkyl and C_{3-7} alkyl).

As a result of these amendments, the European application no longer covers velpatasvir.

The European examiner found that, after these amendments, the claimed compounds are novel vis-à-vis the prior art, but lack an inventive step.

In a second round of amendments (dated 24.07.2014), the applicants argued that the modification of the pyrrolidine ring can impact on the antiviral activity of the compounds, as supported by biological assays used to analyse the antiviral potency (EC_{50}) of the said compounds.

The application is still under examination.

In another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent and a pharmaceutically acceptable carrier or excipient. The therapeutic agent used in combination with the claimed compound can be interferons, ribavirin and analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants and non-nucleoside inhibitors of HCV.

Finally, the invention also relates to general methods of making the claimed compounds and intermediates thereof.

Observations

The PCT application covers velpatasvir, which is specifically claimed in claim 41 of the PCT application (velpatasvir is structure 8 in a list of 23 compounds characterized by their chemical structure).

However, in the European phase, the applicants have subsequently limited the compounds claimed to only one of the five classes of compounds in the PCT application. As a result, in Europe this application no longer concerns velpatasvir.

The pending or granted claims in countries outside the European Union will need to be monitored and checked in order to determine whether or not the application/patent in a given country covers velpatasvir.

Patent 2

Title: Condensed imidazolylimidazoles as antiviral compounds.

WO-A-2013/075029 (*Gilead Pharmasset, filed 16.11.2012*); **EP-A-2635588**

Summary

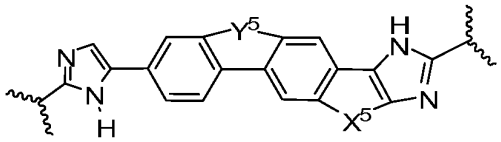
This is the basic compound patent covering velpatasvir. The patent claims velpatasvir (the API) as well as pharmaceutical compositions comprising it and its combination with other HCV agents.

This patent would likely block generic market entry in the countries where it is in force.

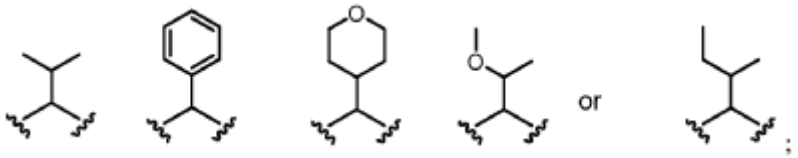
Description

The claimed compounds are a selection from the first class of compounds of formula (I) of PCT application WO-A-2012/068234 (patent 1). They correspond to the first class of antiviral compounds of patent 1.

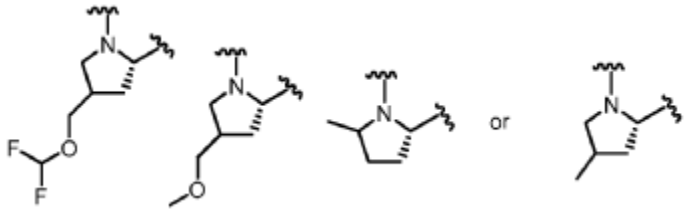
The PCT application provides a compound of formula (I): E^{1a}-V^{1a}-C(=O)-P^{1a}-W^{1a}-P^{1b}-C(=O)-V^{1b}-E^{1b} in which W^{1a} is:



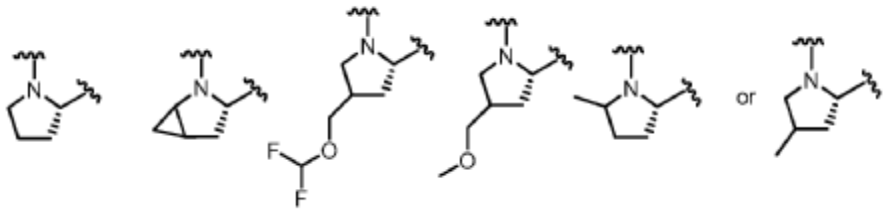
and is optionally substituted with one or more groups independently selected from halo, alkyl, haloalkyl or cyano; and in which Y^5 is -O-CH_2- or -CH_2-O-; X^5 is -CH_2-CH_2- or -CH=CH-; E^{1a} is -N(H)(alkoxycarbonyl), N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or E^{1a}-V^{1a} taken together are R^{9a}; E^{1b} is -N(H)(alkoxycarbonyl), -N(H)(cycloalkylcarbonyl) or -N(H)(cycloalkyloxycarbonyl); or E^{1b}-V^{1b} taken together are R^{9b}; V^{1a} and V^{1b} are each independently selected from:



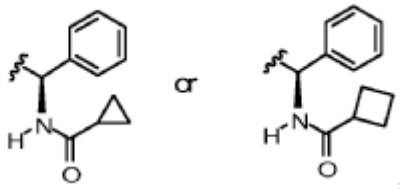
P^{1a} is selected from:



P^{1b} is selected from:



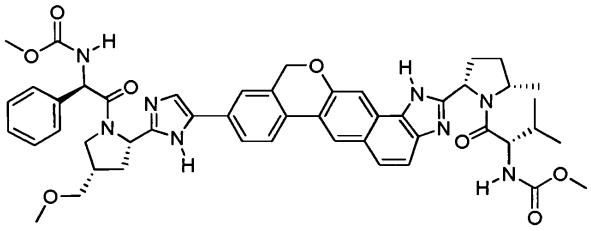
R^{9a} and R^{9b} are each independently:



The compounds possess a pentacyclic ring system linked to an imidazole ring, and both the pentacyclic ring system and the imidazole ring are linked to a substituted pyrrolidine.

The International Searching Authority acknowledged the novelty and inventiveness of the claimed subject matter. However, it was found that the claims cover a large number of compounds and the description does not provide enough evidence that all of them possess the claimed function.

On entry into the European phase, the applicants filed an amended set of claims where the compounds claimed were limited to the specific compound or salt thereof of pending claim 12: velpatasvir.



The application has received an intention to grant (09.01.2015).

The applicants have filed a divisional which is due to be published shortly (application Nº: EP15156617.1).

The present application also provides a pharmaceutical composition comprising claimed compounds or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier. Additionally, the present application also discloses a pharmaceutical composition for use in treating HCV. In a further embodiment, the composition comprises at least one additional therapeutic agent for treating HCV; the said therapeutic agent being selected from ribavirin, an NS3 protease inhibitor, a nucleoside or nucleotide inhibitor of HCV NS5B polymerase, an alpha-glucosidase 1 inhibitor, a hepatoprotectant, a non-nucleoside inhibitor of HCV polymerase, or combinations thereof.

In a preferred embodiment, the compound of formula (I) is methyl{(2S)-1-[(2S,5S)-2-(9-{2-[(2s,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7}naphtha[1,2-d]imidazole-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate (GS-5816, velpatasvir) and the inhibitor is sofosbuvir.

Finally, the invention discloses general methods of making the claimed compounds and the intermediates thereof.

Observations

The applicants have filed a divisional at the European Patent Office which is due to be published shortly (application Nº: EP15156617.1).

Patent 3

Title: Hepatitis C treatments with sofosbuvir

WO-A-2014/185995 (*Gilead Pharmasset, filed 30.01.2014*)

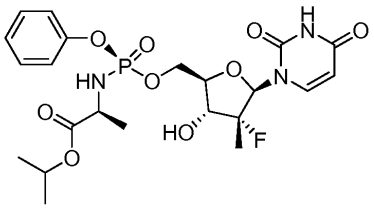
Summary

This application relates to combinations of specific compounds, including the combination sofosbuvir/velpatasvir and sofosbuvir/ledipasvir.

Description

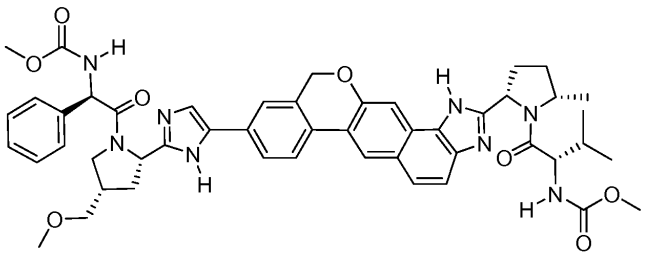
This application relates to combinations of specific compounds, designated in the application as compounds I – V and characterized by both chemical names and structures (see below), with sofosbuvir. According to this application, pharmacokinetic parameters (e.g. C_{max}, AUC_{inf} and AUC_{last}) of sofosbuvir were improved when sofosbuvir was administered along with one or more of compounds I – V. When co-administered with one or more of these compounds, the dose of sofosbuvir needed for treating hepatitis C may be reduced.

Sofosbuvir:



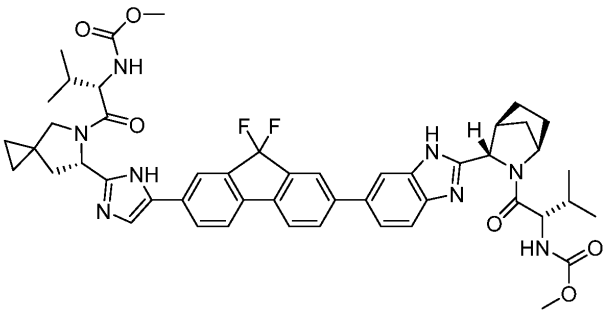
(S)-isopropyl 2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino) propanoate.

Compound I:



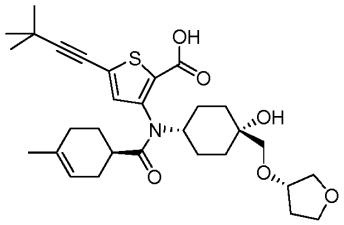
Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate (this is GS-5816 or velpatasvir);

Compound II:



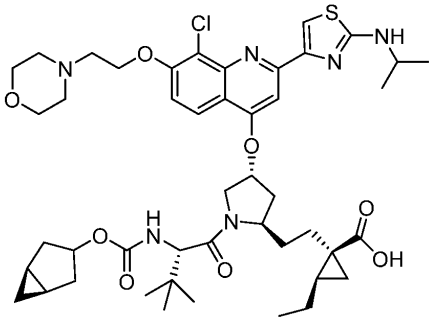
Methyl ((S)-1-((1R,3S,4S)-3-(6-(9,9-difluoro-7-(2-((S)-5-((methoxycarbonyl)-L-valyl)-5-azaspiro[2.4] heptan-6-yl)-1H-imidazol-5-yl)-9H-fluoren-2-yl)-1H-benzo[d]imidazol-2-yl)-2-azabicyclo[2.2.1]heptan-2-yl)-3-methyl-1-oxobutan-2-yl) carbamate (this is GS-5885 or ledipasvir).

Compound III:



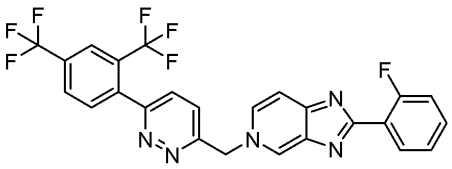
5-(3,3-dimethylbutyn-1-yl)-3-[(*cis*-4-hydroxy-4-{[(3S)-tetrahydrofuran-3-yloxy]methyl}cyclohexyl){[(1R)-4-methylcyclohex-3-en-1-yl]carbonyl}amino] thiophene-2-carboxylic acid (or GS-9669).

Compound IV:



(1R,2R)-1-((2S,4R)-1-((2S)-2-(((((1R,5S)-bicyclo[3.1.0]hexan-3-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)-4-((8-chloro-2-(2-(isopropylamino)thiazol-4-yl)-7-(2-morpholinoethoxy)quinolin-4-yl) oxy)pyrrolidine-2-carboxamido)-2-ethylcyclopropane-1-carboxylic acid (or GS-9451).

Compound V:



5-((6-(2,4-bis(trifuoromethyl)phenyl)pyridazin-3-yl)methyl)-2-(2-fluorophenyl)-5H-imidazo[4,5-c]pyridine (GS-9190 or tegobuvir).

The application also provides a pharmaceutical composition comprising a compound selected from compounds I – V and sofosbuvir, together with one or more pharmaceutically acceptable carriers or excipients. This composition comprises an effective amount of a compound selected from compounds I – V or a combination thereof, and an effective amount of sofosbuvir, in which the amount of sofosbuvir is about 350 mg daily or less; the administration is for a period that is no longer than about 8 weeks.

Additionally, the composition can further comprise the administration of another therapeutic agent for treating HCV (e.g. interferons, ribavirin or analogs, HCV NS3 protease inhibitor, alpha-glucosidase 1 inhibitor, hepatoprtectants, nucleoside or nucleotide inhibitor of HCV NS5B polymerase, non-nucleoside inhibitor of HCV NS5B polymerase, HCV NS5A inhibitor). The additional therapeutic agent may also be one that treats other conditions such as HIV infections.

ANNEX 1. Velpatasvir patent situation in countries

The INPADOC patent family members for each of the three patents/applications are listed in the tables below.

Anticipated expiry dates of patent 2 have been provided. It may be noted that expiry dates can differ between countries due to differences in patent term or because the patent application was filed – on a different date – directly at the concerned office (instead of through the PCT route). The indicated expiry dates therefore must be checked in countries that offer patent term extension/restoration (such as European Union countries, Japan and the USA). If velpatasvir is approved for use, it is likely that the innovator will apply for patent term extension/restoration.

	Patent 1	**Patent 2**	**Patent 3**
	WO2012068234A1 **Appl. N°: PCT/US2011/060966**	**WO2013075029A1** **Appl. N°: PCT/US2012/065681**	**WO2014185995A1** **Appl. N°: PCT/US2014/013947**
Applicants	**Gilead Pharmasset (USA)**	**Gilead Pharmasset (USA)**	**Gilead Pharmasset (USA)**
Filing date	**16.11.2011**	**16.11.2012**	**30.01.2014**
Title	**Antiviral compounds**	**Condensed imidazolylimidazoles as antiviral compounds**	**Hepatitis C treatments with sofosbuvir**
Subject matter	**Generic compound patent – constraining for generic medicines where granted.**	**Basic compound patent – constraining for generic medicines where granted.**	**Sofosbuvir/velpatasvir combination with or without another anti-HCV compound**
Priority data	**US 61/414,818 – 17.11.2010** **US 61/504,924 – 06.07.2011**	**US 61/560,654 – 16.11.2011**	**US 61/824,266 – 16.05.2013** **US 61/919,108 – 20.12.2013**
African Regional Intellectual Property Organization*			
Argentina	Appl. N°: 2011PI04276 Publ. N°: 083711A Status not available		
Australia	2011328980A1 Under examination	2012318253A1 Under examination	
Brazil			
Canada	2817840A Under examination	2815082A allowable Expiry: 16.11.2023	
		2884712A1 (divisional) Under examination	
Chile		Publ. N°: 2013001428A1 Status not available	
China		Appl. N°: 201280004097 Publ. N°: 103328480A Under examination	
China, Hong Kong SAR			
Colombia			
Costa Rica		20130231A Status not available	
Croatia			

	Patent 1	Patent 2	Patent 3
Dominican Republic			
Eurasian Patent Office*		201390576A1 Status not available	
Ecuador		Appl. N°: 2013SP12790 Publ. N°: 13012790A Status not available	
Egypt			
El Salvador			
European Patent Office*	Appl. N°: 11791700 Publ. N°: 2640719A Under examination	Appl. N°: 12798525 Publ. N°: 2635588B Expiry date: 16.11.2032	
		Divisional: EP15156617 (not yet published)	
Guatemala			
Honduras			
India			
Israel	226346 Under examination	226345 Under examination	
Japan	Appl. N°: 2013-539970A Publ. N°: 2013-542996A Under examination	Appl. N°: 2014-542523A Publ. N°: 2015-512860A Under examination	
Mexico		2013005575A Status not available	
Moldova		Appl. N°: a 2013 0029 Publ. N°: 013-0029A Status not available	
Morocco		Appl. N°: 20130036 Publ. N°: 34727B1 Status not available	
New Zealand			
Norway			
Pakistan+			
Peru		Appl. N°: 1207-2013/DIN Publ. N°: 1163-2014A Under examination	
Philippines			
Republic of Korea	Appl. N°: 1020137015201 Publ. N°: 1020140033316A Under examination	Appl. N°: 1020137015198 Publ. N°: 1020140096239A Under examination	
Russia			
Serbia			
Singapore	Appl. N°: 201303622 Publ. N°: 190785A Under examination		
South Africa			
Thailand+			

	Patent 1	Patent 2	Patent 3
Ukraine		Appl. N°: a201306068 Status not available	
Uruguay	Appl. N°: 20110033735 Publ. N°: 33735A Status not available		
USA	Appl. N°: 13/884,578 Publ. N°: 20140018313A Notice of allowance (24.04.2015)	20130177530A1 – 8575135B2 20130156732A1 – 8940718B2 20140112885A1 – 8921341B2 13/679,862 – 20130164260A1 Application abandoned (30.05.2014) 14/261,325 – 20140309432A1 Under examination	Appl. N°: 14/169,004 Publ. N°: 20140343008A Under examination
Viet Nam+			

Notes:
Cells in grey colour indicate that no patent or patent application has been found in the INPADOC database or – in the cases of Pakistan, Thailand and Viet Nam – during the check at the National Patent Office. This may mean that no patent application was filed, that the application has not been found (e.g. in the case of clerical error), or the application had not been published at the time of the search. Information in this Annex should therefore always been checked at the relevant patent office.

***African Regional Intellectual Property Organization (ARIPO):** Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, São Tomé and Príncipe, Sierra Leone, Somalia, Sudan, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.

*** European Patent Office (EPO): *designated contracting states*:** Austria, Belgium, Bulgaria, Switzerland, Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, United Kingdom, Greece, Hungary, Ireland, Iceland, Italy, Liechtenstein, Lithuania, Luxembourg, Latvia, Monaco, Malta, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, San Marino, Turkey; ***Extension states*:** Albania, Bosnia & Herzegovina, Croatia, Montenegro, Macedonia (former Yugoslav Republic of Macedonia), Serbia.

*** Eurasian Patent Organization (EA):** Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyz Republic, Moldova, Russian

Federation, Tajikistan and Turkmenistan.

+ Confirmed in checks at the local patent office.

ANNEX 2. Patent application filing dates

Patent 1: EP-A-2640719 – WO-A-2012068234 (*Gilead, filed 16.11.2011*)

Legal status of the equivalents:

PATENT/APPLICATION NUMBER	FILING DATE	LEGAL STATUS
WO 2012/068234	PCT filing: 16.11.2011	
EP-A-2640719*	National entry:	GRANTED
AR-A-083711	Filing date: 16.11.2011	Not available
AU-A-2011-328980	Filing date: 16.11.2011 National entry: 03.04.2013	Under examination
CA-A-2817840	National entry: 13.05.2013	Under examination
IL-A-226346	National entry: 13.05.2013	Not yet examined
JP-A-2013-542996	Filing date: 09.07.2013	Not available
KR-A-20140033316 KR-A-1020137015201	Filing date: 13.06.2013	Not yet examined
SG-A-190785	National entry: 10.05.2013	Under examination
TW-A-201240990	National entry: 16.11.2011	Not available
US-A-2014-0018313	Filing date: 16.01.2014	Under examination
UY-A-33735	National entry: 16.11.2011	Not available

* Designated contracting states: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR. Extension states: BA, ME.

Patent 2: EP-B-2635588 – WO-A-2013/075029 (*Gilead Pharmasset, filed 16.11.2012*)

Legal status of the equivalents:

PATENT/APPLICATION NUMBER	FILING DATE	LEGAL STATUS
WO 2013/075029	PCT filing: 16.11.2012	
EP-B-2635588*	National entry: 04.06.2013	GRANTED
EP15156617.1		divisional
AU-A-2012-318253	Filing date: 03.04.2013	Under examination
CA-A-2815082	Filing date: 16.11.2012 National entry: 13.05.2013	Under examination
CL-A-2013-01428	Filing date: 17.05.2013	Under examination
CN-A-103328480	National entry: 09.06.2013	Under examination
CR-A-2013-0231	Filing date: 17.05.2013	Not available
EA-A-2013-90576**	Filing date: 16.11.2012	Not available
IL-A-226345	National entry: 13.05.2013	Under examination
JP-A-2014-542523	National entry: 10.05.2013	Not available
KR-A-10-2014-0096239	National entry: 13.06.2013	Unexamined
MA-B-34727	Filing date: 10.06.2013	Not available
MD-A-2013-0029	National entry: 16.05.2013	Under examination
MX/a/2013/005575	Filing date: 17.05.2013	Not available
PE-A-1163-2014	National Entry: 17.05.2013	Under examination
US-B-8575135 US-B-8921341 US-B-8940718 US-A-2013-0164260 US-A-2014/0309432	Filing date: 01.03.2013 Filing date: 08.10.2013 Filing date: 16.11.2012 Filing date: 16.11.2012 Filing date: 24.04.2014	Cont. of US' 718 Cont. of US' 135 Expiry date: 16.11.2032 Abandoned (30.05.2014) Cont. of above application

* Designated contracting states: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR. Extension states: BA, ME.

** EA: Eurasian Patent Office (Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan, Turkmenistan).

Patent 3: WO-A-2014/185995 (*Gilead Pharmasset, filed 30.01.2014*)

Legal status of the equivalents

PATENT/APPLICATION NUMBER	FILING DATE	LEGAL STATUS
WO 2014/185995	PCT filing: 30.01.2014	
US-A-2014-0343008	Filing date: 30.01.2014	Under examination

* Designated contracting states: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR. Extension states: BA, ME.